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DATA ON THE PHARMACOLOGY AND TOXICOLOGY OF THE BRAIN  
OBTAINED BY THE CONDITIONED REFLEX METHOD

(A Review of Soviet Literature)

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For a long time the study of the mechanism of the action of drugs on higher nervous activity has developed most slowly of all the branches of pharmacology. The psychological method of subjective analysis of phenomena with transfer of results "by possible analogy" to animals of other types or to other individuals has created considerable obstacles to objective perception of the higher cerebral functions. Using the conditioned reflex method to study physiology was a great advance, as also in the case of the pathology of higher nervous activity.

The author of the conditioned reflex theory, the brilliant physiologist, I. P. Pavlov, said quite correctly that "the brain, in its highest form, the human brain, has created and is in the process of creating natural science and is itself the object of study of natural science."

Advances in the physiology of the cerebral cortex enabled Pavlov to carry on many investigations in his study of the effect of various drugs on higher nervous activity. These investigations, continued by his many colleagues, have received enthusiastic support in a number of foreign textbooks on pharmacology (for example, Clark, Goodman and Gilman, McGuigan, et al.), as well as in Russian handbooks on the subject.

However, at the present time we still do not have a complete summary of the data obtained, although such a work would promote greater interest among pharmacologists in this problem (some problems were dealt with by A. A.

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Lidbachev in his article in *Farmakologiya*, Vol. 7, No. 1, 1938). The brief review given here was written for this purpose. It should be clear from the beginning, however, that the study of drugs by the conditioned reflex method does not cover the entire mechanism of their effects on the central nervous system.

Pavlov's colleagues' studies threw an entirely new light upon the mechanism of the action of bromine, radically changing our ideas on the depressive action of bromine on the higher nervous centers. The first articles on the study of the action of bromine by the conditioned reflex method (P. M. Nikiforovskiy) showed the complexity of the action of bromine.

Subsequently M. A. Petrova, L. N. Fedorov, O. P. Yakovleva, F. P. Mayorov, M. A. Usiyevich, et al., working with dogs with experimental neurosis and a predominance of stimulative processes, succeeded in restoring the equilibrium of nervous processes by the effect of bromine when the inhibitory process seemed to have disappeared completely.

However, an increase in the excitability of the cortex was sometimes observed in other experiments (increase in the positive reflexes--M. A. Petrova). Pavlov's school explained this phenomenon by the stimulation of positive induction in the initially strengthened inhibitory process. The bromides also proved effective in a hypnotic state, which, in Pavlov's opinion, is excessive inhibition. Bromine acted favorably here and dissipated the hypnotic state (M. A. Petrova, O. P. Yakovleva, L. N. Fedorov, F. P. Mayorov). This effect was also explained by Pavlov's school by the effect of bromine on the inhibitory process. In this case bromine, strengthening the inhibitory process, appears to concentrate "in our artificial and specific vital inhibitory centers," precisely as a result of increasing its strength, since it has been established that "the inhibition not only irradiates but also concentrates, and its concentration increases with development and increase of the inhibition."

The mechanism of the action of bromine is clearly seen in the study of the effect of the various doses in dogs having various types of nervous system. S. I. Gal'perin, M. A. Petrova, F. A. Usiyevich, A. A. Lindberg, S. D. Emamiyev, and F. P. Mayorov have been active in this field. Small doses of bromine have a strengthening effect on the inhibitory process but this strengthening is slight and does not induce the opposite process (stimulation). In such a case, we see only the inhibitory effect of bromine (the force of the conditioned reflexes is diminished). In a stimulative type this effect is manifested in an acceleration in the development of the conditioned reflexes.

Large doses considerably increase the strength of the inhibitory process. The induction of the opposite process of stimulation corresponds to this strengthening of inhibitory process. The increase in conditioned reflexes and retardation of their diminution sometimes noted under the influence of bromides is also explained in this way.

Very large doses of bromine, which strengthen the inhibitory process excessively, cause irradiation of this process (S. I. Gal'perin) which is reflected in loss of conditioned reflexes. A great deal of research was conducted on the action of bromine in a prolonged administration during the castration of dogs (M. A. Petrova, O. P. Yaroslavtseva), monkeys (A. A. Eam), on the senile nervous system in dogs (A. M. Pavlov, M. A. Usiyevich), in children (N. I. Krasnogorskiy), under conditions of training inhibitory processes (O. P. Yakovleva), at the time of introduction and aspiration of bromine from an organism (A. N. Georgiyevskaya, M. A. Usiyevich). These studies support the view of the particular effect of bromine on the inhibitory process in the sense of strengthening it.

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The effect of caffeine has been studied by the conditioned reflex method in no less detail. The effect of caffeine upon the processes of stimulation was unmistakable from the very beginning of the study. I. V. Zavadskiy observed a decrease in the latent period and an increase in the positive conditioned reflexes. P. M. Nikiforovskiy pointed out that the conditioned inhibition lost its properties, and observed a release of conditioned reactions. Others (Zeval'd, Dolin, Mayorov) noted that with the action of caffeine the specific traces of a conditioned stimulus disappeared, and the process of diminution of the reflexes was retarded. But, along with these phenomena, a balancing phase was sometimes observed when both strong and weak external conditioned stimuli brought about the same results (N. V. Zinkin), so that the relationship between the strength of the reflex and the intensity of the stimulus was undermined.

In A. A. Lindberg's doctoral dissertation, he investigated the relation between the effect of caffeine and the dose. It developed that large doses of caffeine may cause a mild decrease in positive conditioned reflexes. The author discusses increasing the excitability of the nervous elements by the effect of caffeine, while at the same time, not increasing functional capacity to any extent. This leads to depletion of the cell reserve.

Shortly afterward Zeval'd reported on the analogous relationship he observed between a dose of cocaine and the magnitude of the conditioned reflexes. He says that prolonged increase of the activity of the cell by acceleration of the dissimulation processes leads to depletion of their working capacity, as a result of which they sink into a defensive, so-called supraliminal, inhibition. A. O. Dolin made a comparative study of the action of caffeine on dogs with various types of nervous system. In the inhibited type the caffeine brought about a considerable increase and greater stability of conditioned reflexes. In the stimulative type, inhibitory phenomena also appeared as a result of the excessively stimulative effect of caffeine (supraliminal inhibitory phenomena).

These experiments show the well-known relationship between the effect of a poison and the specific features of an organism, and they confirm the truth of the previously explained assumption on the mechanism of the action of caffeine.

In bromine and caffeine, according to Pavlov, we have something resembling two drives for two basic nervous processes: "Bromine for inhibition, caffeine for stimulation." Application of this combination in tests during experimental neurosis restored equilibrium for a long period in cases where the action of bromine alone proved insufficient. (E. K. Petrova, A. M. Pavlova, Zeval'd, et al.). However, it is necessary to consider the strength of the central nervous system and the nature of both processes and to vary the doses of bromine and caffeine accordingly. The stimulative process is somewhat heightened by small doses of caffeine, but not beyond the supraliminal, and does not deplete the cells. Along with this, under the influence of bromine the internal inhibitory processes are strengthened, whereby an equilibrium of both processes is restored. For a long time there was no unanimous opinion on the mechanism of original stimulation caused by small doses of alcohol. Some, like Bergman, Bins, and Kraepelin, considered this stimulation to be actual, and others joined in the opinion previously advanced by Schmiedeberg that this stimulation was caused by paralysis of the known cerebral centers. The effect of alcohol was not clarified by the conditioned reflex method (I. V. Zavadskiy, P. M. Nikiforovskiy, A. A. Lindberg, S. N. Rotekhin, et al.) In the very beginning of the experiment, a slight decrease was noted in the magnitude of the positive conditioned reflexes. This signified a weakening of the stimulative processes. This release of the inhibitory reflexes in this case was explained by Pavlov as a weakening of the internal inhibitory processes.

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The pallium of the cerebral hemispheres of children are very sensitive to alcohol. N. I. Krasnogorskiy observed an immediate lowering of the conditioned reflexes and a release of the inhibitory reactions under these conditions.

Large doses of alcohol always brought about a decrease not only in the magnitude of all positive conditioned reflexes, but also in the unconditioned, which indicates an inhibitory effect on the subcortical formations. Evidently the alcohol acts on the processes of internal inhibition, and, along with this, there occurs at first a weak then gradually deepening inhibition of the stimulative processes. This mechanism of the action of alcohol appears very clear in contrast with its effect on animals with various types of nervous systems, which was produced by A. O. Dolin. When alcohol is given to the inhibitory type, it decreases the inhibitory processes and increases alimentary stimulation (extirpation of the inhibitory effect of the cortex from the sub-cortex). With an excitable animal, alcohol can cause complete disappearance the conditioned reflexes, and development of the general inhibitory phenomena. According to the data of M. K. Petrova and L. A. Andreyev, a single dose of alcohol can cause changes in nervous activity which last for several days or weeks, while normal activity is only gradually restored.

With extensive administration of alcohol there is at first a weakening of the inhibitory process, and then of the stimulative process. Both processes become progressively inert, and eventually the dogs pass into a hypnotic state. Small doses of alcohol administered to weaken inhibition improved the conditioned reflex activity of dogs considerably in this particular case (M. K. Petrova). The pathological state of the cortex was sometimes manifested by an experimental phobia and sometimes a state similar to the hallucinations of an alcoholic.

In recent years, thanks to the conditioned reflex method, our ideas on the mechanism of the action of soporifics have been considerably broadened. In the course of this development the similarity of their effects to those of alcohol was also disclosed; but along with this similarity there are also differences in the quantitative and temporal aspects of the action. The effect of chloral hydrate on dogs was studied in detail by V. K. Fedorov and S. P. Levin, and on children by N. I. Krasnogorskiy. They observed the irregular effect of small doses of chloral hydrate, and a regular decrease in the conditioned reflexes with large doses. V. K. Fedorov concludes from his experiments that with small doses of chloral hydrate the inhibitory process is weakened. This process is noticed before the stimulative process. However, first of all there is a loss of concentration, irradiation in the cerebral hemispheres, and possible permeation into the lower systems. Using chloral hydrate in a case with an inhibitive reflex, V. K. Fedorov found a dose of soporifics that would not affect the stimulative process but would completely upset the inhibitory process. Moreover, the initial factors of the stimulus took on a positive value. Consequently, chloral hydrate was adequate enough to destroy the conditioned inhibitions, and thereby obstructed the adaptability of the organism to the surrounding medium. In Fedorov's opinion, sleep induced by chloral hydrate is caused by irradiation of the inhibitory process, which, along with a decrease in intensity, loses its effect. With large doses the stimulative processes are decreased, and ultimately the nerve cells fail to respond under the toxic effects.

Chloral hydrate can not destroy supraliminal inhibition, but on the contrary, it may create conditions very favorable for its appearance, as a result of inhibiting the functions of the pallium.

Chloral hydrate has a strong hypnotic effect on the subcortical centers (stronger than alcohol), which is manifested by a decrease in the unconditioned reflexes (N. I. Krasnogorskiy).

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The effect of luminal on conditioned reflexes was studied by M. K. Petrova and S. P. Levin on physically weakened castrated dogs after experimental inhibitory neurosis had been induced. As it developed, luminal did not remove or weaken the phenomena of dispersed inhibition and was able to restore the disturbed equilibrium.

Moreover, sometimes it was possible to detect a period of some initial stimulation in animals. M. K. Petrova was inclined to regard this phenomenon as a struggle between the stimulative effect of conditioned stimuli and the inhibitory effect of luminal. On the whole, luminal has an effect like chloral hydrate, removing the inhibitory process of concentration and permitting irradiation, thereby causing sleep.

Veronal has an effect similar to luminal (A. A. Lindberg). A very favorable effect of veronal on dogs with experimental neurosis was observed by M. K. Petrova: it showed a beneficial effect regardless of nervous type, age, and degree of depletion of the nervous system. The same favorable effect of veronal was obtained in I. P. Pavlov's psychiatric clinic, headed by Professor A. G. Ivanov-Smolenskiy. A. A. Lindberg studied the effect of neodorm and ethyl alcohol but he did not note any specific features.

The effects of bromine and soporifics were directed to inhibition in this way, and it was proved that bromine strengthens and concentrates inhibition while the soporifics have a directly opposite effect. Bromine, as was pointed out above, neutralizes the stimulative processes with the inhibitory processes on a new level. These soporifics, it must be supposed, do not affect the power of the inhibitory process, but affect its extent and dispersion as well as the simultaneous inhibition of the stimulative processes.

The effect of valerian on the central nervous system remains unexplained. A. A. Baum's research on a marmoset monkey under conditions of experimentally induced neurosis with shifting of the positive stimuli to the negative threw some light on the subject. Under conditions of neurosis with a predominance of stimulative processes, valerian proved a positive agent in the sense of restoring the equilibrium of the stimulative and inhibitory processes. When the cortex was in a normal condition, the valerian had no effect on it.

Very little work has been done on the effect of morphine on conditioned reflex activity. It is evident from the work of Zavadskiy and Potekhin that conditioned and unconditioned reflexes initially diminished under the influence of morphine and finally disappeared completely.

Potekhin explains that a decrease in conditioned alimentary reflexes by morphine administration in a given case was due to stimulation of the emetic center, which brings about an inhibition of the alimentary center. This author explains the effect of apomorphine analogously.

Some attention should also be given to the effect of calcium chloride on conditioned reflexes. It was observed that it strengthens the inhibitory processes and promotes the development of inhibitory reflexes. This mechanism clearly appears in the administration of calcium chloride to dogs with experimentally induced neurosis with a predominance sometimes of stimulation and sometimes of inhibition. According to M. K. Petrova's data, in the case of a neurosis with a predominance of stimulative processes, when all forms of internal inhibition had disappeared, calcium chloride not only restored inhibition but also evoked a somnolent state, which was not generally characteristic of the experimental dog under the conditions of the experiment. L. N. Fedorov also succeeded in restoring an unbalanced equilibrium in dogs with experimental neurosis with a predominance of stimulative processes where the bromine did not have the desired effect. In A. A. Baum's and M. K. Petrova's experiments on dogs with inhibitory neurosis, somnolence set in even after the administration of calcium chloride, but the equilibrium was not restored. The effect

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on the dog with stimulative experimental neurosis depends upon the dose. Small doses administered for short periods were effective for a comparatively long period, restoring the unbalanced equilibrium and not causing much subsequent stimulation. Large doses established equilibrium for shorter periods than small doses, and from then on sharply increased the stimulative phenomena (in comparison with the initial conditions).

A very favorable sedative effect on a dog with stimulative neurosis was obtained by M. I. Petrova and L. N. Fedorov, using calcium bromide. This compound showed a rather stable result in cases where bromides and calcium chlorides, taken separately, did not show a beneficial effect on dogs with experimental neuroses. A prolonged administration of calcium bromide may greatly lower the whole tone of the cortical processes. The addition of caffeine in these cases may achieve a complete cure of dogs with experimental neuroses.

Laminskij reported in 1943 on the use of a method of conditioned reflexes to illustrate the mechanism of the action of antipyretics -- sodium salicylate, aspirin, antipyrine, pyramidon, and phenacetin. These drugs did not have a very depressing effect upon conditioned reflex activity.

N. I. Krasnogorskiy noted that aspirin had a very weak effect on conditioned reflexes in children.

Bulbo-capnine, investigated by V. S. Daryabin by the conditioned reflex method, did not have a marked effect on conditioned reflexes in small doses. With an increase in the dosage, the alimentary reflexes were the first to be inhibited, and only after the complete disappearance of the alimentary conditioned reflexes did inhibition of the motor reflexes set in. The phenomena of catalepsy and negativism developed with a high degree of poisoning.

After poisoning, recovery proceeded in the reverse order, and finally the alimentary conditioned reflex mechanism was restored.

Carbonic acid showed a clearly depressing effect on the pallium of human beings and decreased their responses. The cortex proved more sensitive to carbonic acid than the subcortical centers, the action of which is still proceeding normally when the effect is already clearly apparent on the skin. The above-mentioned effect of carbonic acid was studied by N. I. Krasnogorskiy in connection with the conditioned reflex activity in children. He also studied the effect of ammonia and oxygen.

In these experiments ammonia was administered by inhalation. The first dose of ammonia, which irritated the child's mucous membrane, acted as a simple inhibitor and inhibited the reflexes. Then, as it permeated the organism, it showed a stimulative effect on the cortex and the subcortical centers as well, increasing the conditioned and unconditioned reflexes.

Oxygen inhalation, which slightly increases the response of the pallium, has a favorable effect on its activities. The conditioned reflexes are increased and the inhibitory stimuli have a more complete effect.

The effect of nicotine on higher nervous activity (I. N. Zhuravlev) when administered in small doses increases the stimulative and weakens the inhibitory processes, but with large doses the alimentary stimulation is lowered to the extent that animals refrain from eating. On the basis of these experiments Zhuravlev concludes that the effect of nicotine amounts to a weakening of the inhibitory process and potential strengthening of the stimulative processes. Due to large doses, there is a marked inhibition of the stimulative processes. Krasnogorskiy noted the stimulative effect of nicotine fumes on conditioned reflexes in children in connection with the cerebral cortex.

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Novikov observed that with small doses of nicotine nervous equilibrium was affected in regard to the predominance of inhibitory processes. Moderate doses disrupted the relationship of the magnitude of the conditioned effect to the physiological power of the stimulus (balancing and paradoxical phase). Increase of the dose tended to intensify the inhibitory process to the point of complete disappearance of the alimentary conditioned reflexes. The author considers the inhibition of the conditioned reflexes under the influence of nicotine a supraliminal inhibition. Nicotine creates such a background of responses in the cerebral hemispheres that physiologically powerful stimuli surpass the maximum under these conditions and accordingly cause no conditioned reflex at all (paradoxical phase) or one of negligible magnitude. With intensification of the poisoning both moderate and strong stimuli exceed the maximum and have no effect (inhibitory phase).

In observing the effect of cocaine on conditioned reflexes, I. V. Zavadskiy concluded that its effect was generally similar to that of caffeine but considerably less regular. Sometimes cocaine has a marked stimulative effect without an initial decrease in conditioned reflexes, and sometimes there is an initial decrease and then an increase of conditioned reflexes.

The effect of cocaine was studied in more detail by I. N. Zhuravlev, who observed that cocaine in small and medium doses tends to increase the conditioned and unconditioned reflexes and release the negative reflexes. With increase of the doses up to a certain limit the indicated changes increase in almost direct proportion to the magnitude of the doses, changing to a decrease in the positive conditioned reflexes with transition to toxic doses. I. N. Zhuravlev was inclined to consider that the effect of cocaine consists primarily in decreasing the inhibitory process with almost simultaneous increasing of the stimulative process. Subsequently, the stimulative process is inhibited.

In the effect of strychnine upon conditioned reflex activity, P. M. Nikiforovskiy noted considerable analogy with the effect of caffeine. But the effect of strychnine was studied in more detail by I. N. Zhuravlev, S. D. Kaminskiy, and S. P. Pyshina. It appeared that the effect of strychnine stands in direct relation to the dose and type of nervous activity in dogs. Small doses of strychnine evoke only quantitative changes of the conditioned reflex reactions: all conditioned reflexes, both positive and negative, increase in comparison with the norm. Consequently the tone of both the processes of stimulation and inhibition are improved. With medium doses the initial period of sharp increase of all reflexes, when the relationship to the power of the stimulus is preserved, changes into a balanced period, reminiscent of a parabolic balanced stage. Large doses, after a short time, cause a sharp increase in reactions, bring on a state of general inhibition in the animal, and finally give rise to convulsions. Medium doses leave a reaction for 1 to 2 days, and large ones for 4 to 5 days, in the form of increased reactions. I. N. Zhuravlev, on the basis of his observations, proposed that the effect of strychnine was realized through the sympathetic nervous system as one of the manifestations of its adaptive and trophic effects upon the pallium.

M. K. Petrova made a detailed study of the change in conditioned reflex activity under the influence of a preparation called sympathomimetine, a product of acid hydrolysis of commercial fibrin. In these experiments, sympathomimetine sharply increased the functional properties of the pallium in all the dogs treated. Besides strengthening the stimulative processes, sympathomimetine strengthened and concentrated the inhibitory processes, thus producing a high equilibrium in the nervous activities. The cortical tone was sharply increased in comparison with the normal state. This was manifested by an unusual strengthening of conditioned reflexes; unconditioned reflexes were also strengthened, but to a lesser degree. Sympathomimetine, like bromine and caffeine, must be given in accurate doses, relative to the state of the nervous system, the age of the animal, and the type of nervous system. A large dose,

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in conformance with the condition of the pallium, may cause supraliminal inhibition, and inhibit conditioned reflex activity. Dogs with neurosis with a predominance of stimulative process under the influence of sympathomimetic quiesced sooner or later; the inhibition lasted sometimes for a long while even after a single dose. Better and more lasting results were obtained with strong, balanced dogs with a high pallium function. In weak, unbalanced, and old dogs the effect either did not last long, or it lasted 1 to 2 days followed by inhibition of the pallium function: conditioned reflex activity decreased, indicating a transition of the pallium to a state of supraliminal defensive inhibition.

It is unfortunately unclear from these experiments to what extent the data obtained are characteristic of stimulation of the sympathetic nervous system and what the result is of the application of a stimulus of nonspecific effect. In G. N. Pribytkova's experiments, the injection of adrenaline increased conditioned reflexes in dogs. V. K. Fadeyeva's recently published data (1946) on increasing the response of the pallium under the influence of phenamine is worthy of attention. Phenamine facilitates the formation of positive reflex connections. The number of previously formed conditioned reflexes increases and their latent period is reduced. Sometimes the release of a simply formed differentiator is observed. These data support the conception of phenamine as a sympathomimetic amine with a predominant effect upon the cerebral cortex.

It is interesting to note the effect of hormones, as products secreted by the endocrine glands and constantly in the organism, on conditioned reflex activity.

The effect of pituitrin was studied by Asratyan, who discovered that it greatly decreased the conditioned reflexes or entirely eliminated them. In A. A. Danilov's research on the effect of pituitrin on the food-salivary and motor reflexes it was noted that its effect depended upon the initial background. With a background of normal conditioned reflex activity pituitrin showed a somewhat negative effect. With a background of a weakening of the inhibitory and stimulative processes, pituitrin had a tonic effect.

M. K. Petrova, B. M. Zavadovskiy and assistants, and G. M. Pribytkova studied the effect of thyreoidin, noting a stimulative effect on the cortex in all cases. Small doses increased the conditioned and unconditioned reflexes, strengthened and concentrated the differentiators, and shortened the latent period. But medium and large doses almost always led to acute disturbances culminating in pathological collapse.

The effect of thyreoidin varied with dogs of various types of nervous system (M. K. Petrova). With the strong type there was an increase in the stimulative process and a decrease in the inhibitory process. With the very first administration of thyreoidin, dogs of the weak type showed sharply decreased conditioned reflexes in connection with the transition of the pallium to supraliminal inhibition, as a result of stimulation which was excessive for weak cells. Then, after a period of decrease, the reflexes showed a period of fluctuation, sometimes with improvement, sometimes with inhibition of the function of the cortex.

With continuous administration of moderate doses of thyreoidin a decrease was observed both in the stimulative and inhibitory processes in the cerebral cortex. A. R. Shastin's research, done in a clinic, on a case of myxedema having a background of decreased conditioned reflex activity, is of interest. Under these conditions the effect was especially apparent in increased conditioned and unconditioned reflexes, with strengthening and concentration of inhibition.

The conditioned reflexes method was used successfully for the same purpose in toxicological experiments in the laboratories of I. P. Pavlov,

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Professor I. S. Tsitovich, and Yu. P. Frolov.

In Tsitovich's laboratory the conditioned reflex method was valuable in determining the harmful effect of doses of benzine and acetone that did not affect the general state of the organism. Thus, it was possible to determine an approximate allowable inactive dose in those who are subjected to prolonged exposures to these poisons under industrial conditions.

Benzine, when inhaled in very low concentrations, in experiments on human beings, showed a depressive effect on the cortex. The latent period of the conditioned reflexes was lengthened, the reflexes themselves lagged, and with an increase in the concentration these conditions vanished completely.

Although very near benzine in toxicity, benzol has a different effect on the central nervous system. In the action of medium concentrations of benzol on dogs the higher nervous activity of the cortex did not lag for long, and the central nerve centers were chiefly affected (tremors of the body, lowering of temperature, uncoordinated gait).

Consequently, the conditioned reflex method enabled us to distinguish the original effect of the poisons in several respects, although in subsequent stages of poisoning, they had symptoms which were very similar to each other.

Acetone, in experiments on dogs, indicated an inhibitory effect on the cortex in high concentrations and decreased conditioned responses. With lower concentrations the conditioned reflexes mainly underwent a differential process (process of inhibition). With a still further decrease in the concentration, the conditioned reflexes, after a relatively rapid decrease, returned to normal, but the differentiators remained low for a long time.

Among the substances studied by the co-workers of Yu. P. Frolov were the cyanide compounds (A. Yu. Izergina, Demidova), an arsenic compound (I. M. Tryakin, A. Yu. Izergina), and carbon monoxide (L. S. Gorseheva).

By poisoning dogs with cyanide compounds, A. Yu. Izergina succeeded in observing an obstruction in the regular alternation of the stimulative and inhibitory processes. The mobility of the nervous processes was obstructed and became more inert. The limit of the functional capacity of the nerve cells was markedly decreased and the slightest strain on the inhibitory process could bring about a collapse of the higher nervous activity with subsequent complete disappearance of the active inhibitory process, and sometimes even the stimulative process. Large doses of cyanide compounds caused dispersed inhibition in the cortex, while even the natural reflexes disappeared. In dogs of the strong type the poisoning terminated in the cortex, and in weak ones it also enveloped the subcortical formations. Restoration to normal proceeded slowly. With strong, unbalanced dogs visible effects disappeared after 2 to 3 hours, and in weak, unbalanced ones, after 3 to 5 days. However, long after the disappearance of visible effects the cortex of the entire brain remained more sensitive to a given poison. This was manifested both in a marked strengthening of the direct reaction upon repeated administration and in a delay in the recuperative period. Izergina treats these phenomena in such a way that a more rapid transition of the pallium to a state of supraliminal inhibition was basically indicated by increased responses, which can be explained by their marked decrease.

Of course, with repeated administration of small doses of poison these obstructions take on a lingering nature, in the form of a reduction in the functional capacity of the pallium and a decrease in the conditioned reflexes, as well as in an inversion of the active relations between the stimuli and reflexes (balancing and paradoxical phases).

The main symptom in dogs with carbon monoxide poisoning is the obstruction in the active inhibitory process. At first, the latent period of the conditioned

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reflexes increases. The fine differentiators are weakened, and the crude ones are preserved for a while. Then the balancing, paradoxical, and ultra-paradoxical phases set in. There is irradiation of the inhibitory process (somnia and sluggishness of the animals). Dogs of the strong type with higher nervous activity proved to have the most resistance to carbonic acid, with a predominance of stimulative processes. In these dogs the first dose of carbonic acid has a somewhat stimulative effect (increase of conditioned reflexes). Dogs of the weak, nervous type are very responsive and have little resistance to carbonic acid.

The effect of a dose of carbonic acid is also distributed over the sub-cortical areas. Chronic poisoning occurred in cycles, and periods of recovery and inhibition alternated with each other (with prolonged effect of the poison). After a period of complete absence of all conditioned reflexes, there was a gradual restoration of higher nervous activity. L. S. Gorskheleva considers the periods of release of the cortex as a defensive inhibition. Recovery also proceeds irregularly. Against a background of gradual improvement, a reversal to toxic phenomena is noted, though less clearly expressed. This process is observed for a long time after the poisoning.

In conclusion, we shall consider the works of I. I. Trynkin and A. Yu. Izergina, which throw some light upon the effect of arsenic on higher nervous activity.

The conditioned and unconditioned reflexes are decreased, and with large doses they disappear. Animals do not eat or even drink. It also developed that in the action of the arsenic the degree of development of the higher nerve centers is the deciding factor. Dogs with the weak, passive type of higher nervous activity showed the most resistance of all animals in the series. It is interesting to note that young puppies and old, decrepit animals are less responsive to poison, and, in phylogenetic order, the more highly developed animals are more responsive to arsenic as far as nerves are concerned.

It is necessary to take notice of a whole group of most interesting studies touching on the effect of various drugs on the development of conditioned reflexes. In 1922 V. A. Krylov published data on the possibility of forming a conditioned reflex by a subcutaneous injection of morphine. In this instance a conditioned connection was formed between the external stimuli accompanying the injection of morphine under the skin and those centers upon which the morphine acts directly through the skin. One rubbing of the injection site gives a picture reminiscent of the effect of morphine: salivation, occasional vomiting, sleep.

An analysis of the connection which forms in association with a conditioned reflex to morphine was made in the work of I. I. Zborovskaya in connection with the act of vomiting and in the work of I. I. Zborovskaya and A. O. Dolin in connection with panting.

The conditioned reflex to poison is subject to all the laws established by the Pavlov school for conditioned reflexes in general. These reflexes were called "conditioned reflexes to neutral stimulus." The conditioned reflexes of sleep were obtained upon injection of chloral hydrate, ether, alcohol, and chloroform. With repeated doses of dionine and heroin, Krylov succeeded in obtaining conditioned vomiting and salivation with administration of atropine -- a conditioned salivation and stimulation. He did not succeed in obtaining a conditioned reflex with pilocarpine, codeine, strychnine, or cocaine, but subsequently M. L. Meyerovich obtained a conditioned reflex of a corresponding nature to pilocarpine and sodium bromide in persons under clinical conditions.

The problem of conditioned vomiting as a reaction to apomorphine has been debated for a long time. In 1926 M. A. Pochopayev reported on the possibility of conditioned vomiting in reaction to subcutaneous injection of apomorphine.

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Neither Krylov nor S. I. Lebedinskaya succeeded in obtaining conditioned vomiting in reaction to apomorphine under ordinary conditions. But when apomorphine was injected in combination with atropine or picrotoxine, as in the work of V. V. Savich and S. I. Lebedinskaya, conditioned vomiting quickly developed. The authors concluded from this that for the development of conditioned vomiting, isolated stimulation of a vomiting center with apomorphine is insufficient, and a more extensive action upon the central nervous system by the poison is necessary, and that the tone of the vomiting center should be at a given level. Subsequently, F. G. Dubinin (1936) noted that repeated injection of apomorphine depresses the vomiting center; he also explained by this the failure of several authors in getting conditioned vomiting in response to apomorphine. Dubinin established that conditioned vomiting from apomorphine can be produced by keeping definite intervals between injections and the regular dosage of apomorphine, which, with repeated injections, does not depress the vomiting center.

In the work of E. B. Babakiy and R. Leytes the possibility of obtaining a conditioned response to repeated benzine poisoning was indicated. A. O. Dolin succeeded in obtaining as a conditioned reflex to camphor all symptoms of its unconditioned effect, even to fits of an epileptic nature. The author called this "experimental epilepsy." The work of A. V. Rikkl', who obtained a conditioned reflex of bile discharge with repeated injections of bile, must also be noted.

Krylov attempted to explain the physiological nature of conditioned reflexes to neutral stimuli by referring them to the group of defensive, protective reflexes.

To terminate this review, I should like to emphasize once more the very great possibilities of Pavlov's method of conditioned reflexes as a very delicate and objective method of analyzing changes in higher nervous activity. The results of the study on the effect of various drugs and poisons by this method have the greatest practical and theoretical value and constitute a valuable contribution to world science.

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